REMARKS

Reconsideration is respectfully requested.

Claims 1-50, 66, 70, 73, and 89 have been cancelled. Claims 51-65, 67-69, 71, 72, 74-88, and 90-93 are pending. Applicants also have filed a request for continued examination and supplemental information disclosure statement with this response.

With respect to all amendments and cancelled claims, Applicant has not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicant reserves the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Withdrawn Rejections and Objections

Applicants respectfully thank the Examiner for withdrawing the rejections and objections in the office action dated December 12, 2005.

Declaration Under 37 C.F.R. § 1.131

The Examiner objected to the declaration under 37 C.F.R. § 1.131 previously submitted on July 14, 2004 because the declaration was unsigned. Applicants herewith resubmitted a signed declaration in accordance with 37 C.F.R §1.131, as discussed below.

Information Disclosure Statement.

The Examiner states that reference C10 was not submitted to the Office.

Applicants herewith include a Supplemental Information Disclosure Statement including reference C10. Applicants respectfully request its consideration.

Claim Interpretation

The Examiner states that "the term 'electrode' will be considered as meaning 'a solid support comprising a metallic surface.'"

The Examiner also states that "the term 'shielding' is used here in its everyday meaning, i.e. 'preventing physical contact.' Therefore, 'blocking moieties shielding nucleic acids from the electrode' means any structural elements which prevent contact target and/or probe nucleic acids with the electrode."

Applicants respectfully traverse these interpretations. Applicants do not take a position with respect to the interpretation, as no such position is necessary given the accompanying declaration.

35 USC § 102(e)

Claims 51-58, 60-62, 64-73, 79, 80, 82, 83, 85-89 and 93 stand rejected under 35 USC § 102(e) as anticipated by Wohlstadter et al., US Patent No. 6,066,448 ("Wohlstadter"). Wohlstadter is a continuation-in-part of USSN 08/402,076, filed March 10, 1995, which is a continuation-in-part of USSN 08/402,277, also filed March 10, 1995. Accordingly, the earliest possible priority date available for the disclosure in Wohlstadter is March 10, 1995.

The Applicants herewith submit a Declaration under 37 C.F.R. §1.131 by inventors Thomas J. Meade and Jon F. Kayyem. The Declaration demonstrates that the claimed invention was made prior to the earliest possible March 10, 1995 priority date of Wohlstadter.

To antedate a 35 USC 102(e) reference, the inventors must show possession of a species within a claimed genus. As stated in the MPEP:

> [t]he 37 CFR 1.131 affidavit or declaration must establish possession of either the whole invention claimed or something falling within the claim (such as a species of a claimed genus), in the sense that the claim as a whole reads on it. *In re Tanczyn*, 347 F.2d 830, 146 USPQ 298 (CCPA 1965). MPEP 715.02.

The inventors need not show possession subject matter identical to that of the references.

As further stated in the MPEP:

> a 37 CFR 1.131 affidavit is not insufficient merely because it does not show the identical disclosure of the reference(s) or the identical subject matter involved in the activity relied upon. If the affidavit contains facts showing a completion of the invention commensurate with the extent of the invention as claimed is shown in the reference or activity, the affidavit or declaration is sufficient, whether or not it is a

> showing of the identical disclosure of the reference or the identical subject matter involved in the activity. See *In re Wakefield*, 422 F.2d 897, 164 USPQ 636 (CCPA 1970). MPEP 715.02.

The Declaration and associated Exhibits demonstrate that the claimed invention was made prior to the earliest Wohlstadter priority date. Paragraph 5 of the Declaration summarizes an embodiment of the invention within the scope of claim 51.

The Declaration discloses the production of an array of claim 51 depicted in Exhibit A. Different regions on the array are defined by 8x8 micron squares on the photolithographic mask. The gold surface is the electrode of claim 51. The thiol-$(CH_2)_{16}$-OH is the blocking and linking moiety. When the thiol-$(CH_2)_{16}$-OH is covalently attached to the nucleic acid and the gold surface, it is the linking entity. When the thiol-$(CH_2)_{16}$-OH is attached to the gold surface, and not attached to the nucleic acid, it is the blocking moiety.

The fluorescent complement is an agent that distinguishes between single stranded and double stranded nucleic acids. Dark squares indicate locations where single stranded nucleic acids were ablated off, and light squares indicate where nucleic acid hybrids were present. A montage of images is depicted in Exhibit A.

The declaration outlines that the invention was completed in this country prior to March 10, 1995. Because the claimed invention was made prior to the earliest Wohlstadter priority date, the Wohlstadter reference is not prior art. Applicants respectfully request withdrawal of this ground for rejection.

35 USC § 103(a)

Claims 59, 63, 81, 84 and 85 stand rejected under 35 USC § 103(a) as being unpatentable over Wohlstadter in view of Kayyem et al., U.S. Patent No. 6,096,273 (Kayyem).

In a separate rejection, claims 75-78 and 90-92 also stand rejected 35 USC § 103(a) as being unpatentable over Wohlstadter in view of Kayyem.

As demonstrated above in the response to the rejection under 35 USC § 102(e), Wohlstadter is not a prior art reference. Therefore, Wohlstadter cannot be combined with Kayyem as described by the Examiner in satisfaction of the requirements of 35 USC § 103(a). Accordingly, Applicants respectfully request withdrawal of this ground for rejection.

CONCLUSION

On the basis of the amendments and remarks presented herein, Applicants believe that this application is in a condition of allowance. Applicants respectfully request that the Examiner pass this application to issue, and early notification of such is requested.

If the Examiner has any questions, she is invited to call the undersigned at (415) 781-1989.

Respectfully submitted,

DORSEY & WHITNEY LLP

Dated: May 20, 2005 By: _____

Timothy A. Worrall, Reg. No. 54,552 for
Robin M. Silva, Reg. No. 38,304

Filed Under 37 C.F.R. § 1.34

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PATENT
Attorney Docket No.: A-64411-2
Attorney File No.: 468267-00067

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

MEADE *et al.*

Serial No.: 09/921,645

Filed: August 3, 2001

For: *Metallic Solid Supports Modified with Nucleic Acids*

Examiner: STRZELECKA, Teresa, E.

Group No. 1637

"EXPRESS MAIL" LABEL NO.:
EV 554099109 US

DECLARATION PURSUANT TO 37 C.F.R. § 1.131

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Sir:

We, Thomas J. Meade and Jon F. Kayyem hereby declare as follows:

1. We are the inventors on the above-identified patent application and are familiar with its contents. We have also reviewed the pending claims in this application.
2. We are familiar with the Office Action mailed on November 17, 2003 wherein claims 51-69, 71, 72, and 74-93 were rejected over Wohlstadter et al. (6,066,448) which has an earliest possible priority date of March 10, 1995.
3. All of the ideas detailed in the above-identified application were contemplated in this country prior to March 10, 1995. This is evidenced by the appended documents.
4. One of the goals of the project that led to the filing of the parent application was to create a surface comprising a self-assembled monolayer with single stranded nucleic acids attached (referred herein as probes), and then to answer three questions: first, whether a solution-based complementary strand would bind to the probe; second, would a complementary strand attached to an atomic force

microscopy (AFM) tip bind to the probe, and if so; third, whether or not we could determin the force necessary to "tear apart" the duplex.

5. The experiments started out with the synthesis of the monolayer portion using an HO-$(CH_2)_{16}$-OH to form a molecule with a protected sulfur group (for attachment to a gold surface) on one end, to which a phosphoramidited nucleic acid was attached. The experiments proceeded with the coating of a gold surface with this monolayer-forming material. A photolithographic mask, with 8 x 8 micron squares on it, was then used to cover the gold surface. The surface was then exposed to a photoactivated agent and a mercury arc lamp which resulted in the ablation nucleic acids from the squares not covered by the mask. We then added a fluorescent complement to the surface, and viewed it under a confocal microscope. This resulted in a pattern of "light", e.g. fluorescent, background, where the fluorescent solution based probes were found, and "dark" squares, where the surface-bound single stranded nucleic acid had been ablated off, and therefore no fluorescent probe was detected. A montage of several of these images, made over the course of the experiments, is attached as Exhibit A.

6. With regard to timing of these experiments, the documents attached as Exhibit B are pages from the notebook detailing the synthesis of some of the compounds used in these experiments. (Please note that all experiments not relevant to the present discussion have been redacted, as have all dates.) For example, page 136 documents the conversion of the HO-$(CH_2)_{16}$-OH molecule to the asymmetrical HO-$(CH_2)_{16}$-OAc needed for further reactions. The bottom of page 139 and the top of page 140 show the synthesis of the protected thiol-$(CH_2)_{16}$-OH molecule. the top of page 141 shows the reaction of the protected thiol-$(CH_2)_{16}$-OH molecule added to a phosphoramidite moiety. In conclusion, the invention was completed in this country prior to March 10, 1995.

7. We declare further that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that the making of willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such

willful statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 5-4-05

Thomas J. Meade

Date: _____

Jon F. Kayyem

willful statements may jeopardize the validity of the application or any patent issuing thereon.

Date: _____ _____
Thomas J. Meade

Date: May 18, 2005 _____
Jon F. Kayyem

EXHIBIT A

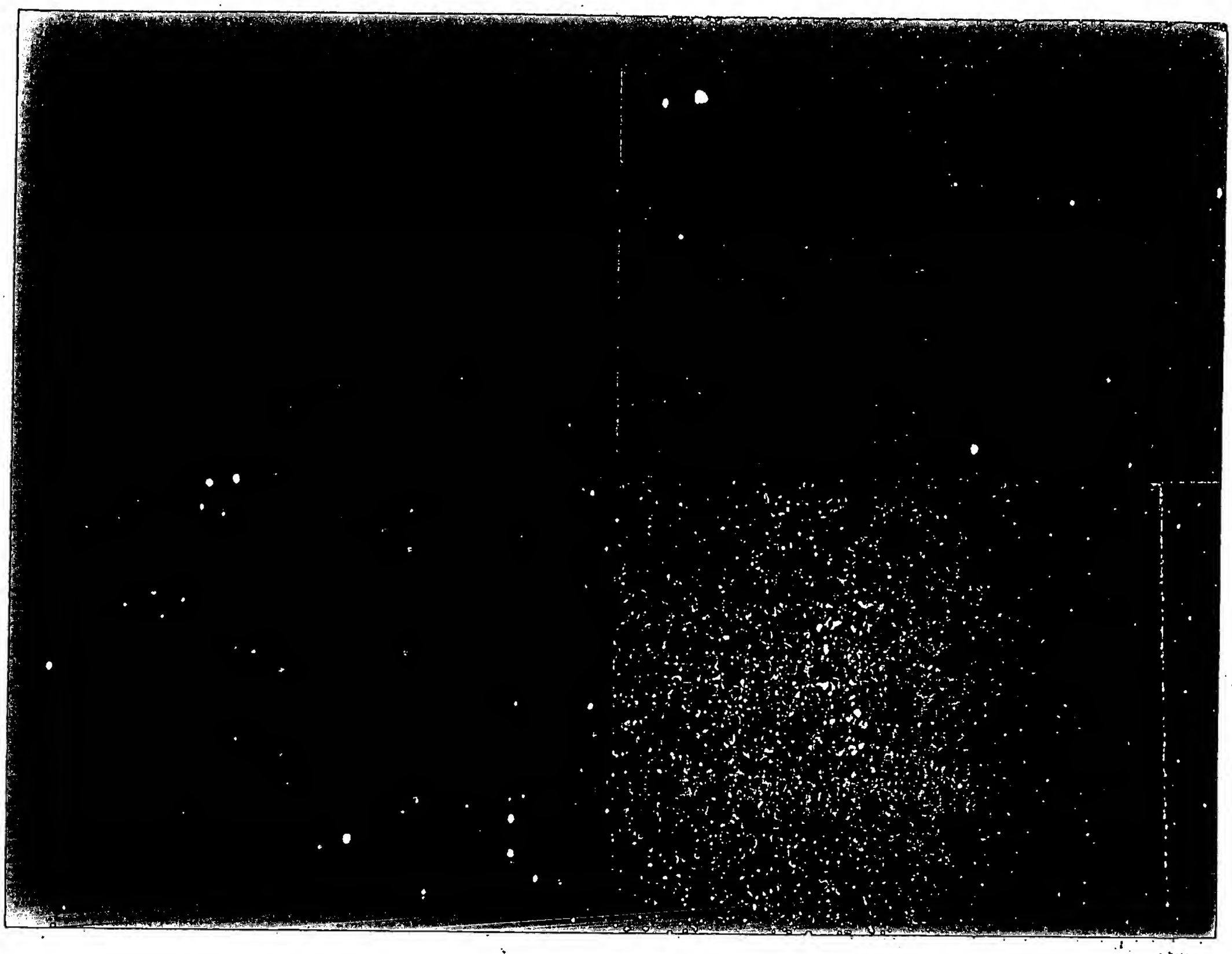


EXHIBIT B

2

$HO(CH_2)_{16}OH \xrightarrow[\text{TEA, } CH_2Cl_2]{\text{1eq. Acetic Anhydride, DMAP}} HO(CH_2)_{16}OAc$

0.5 gr of $HO(CH_2)_{16}OH$ (mw 258.45 ; 1.9×10^{-3} moles) was placed in a small round bottom and 20 mls of CH_2Cl_2 added along with 0.05 equiv (9.7×10^{-5} moles (122.17 or 11.8 mgs) and 1.4 equiv of TEA (417 µl) and 1 equiv of Acetic Anhydride {mw 102.9 ; d = 1.08} {10.57 moles/liter} or 173 µl.

50/50 Ether/Hexane

Diol Std — DMAP Rxn — continuous extract

50/50 ether/Hexane

Rxn. 2

2.05 gr (7.93×10^{-3} moles) was placed in a 100 ml RBF and 60 mls of CH_2Cl_2 added along with 0.05 equiv DMAP (48 mg) and 1.4 equiv of TEA (1.7 mls) and 695 µl of Acetic Anhydride

Reaction 3

$HO(CH_2)_{16}OH$ —(1eq. Acetic Anhydride, DMAP, TEA, CH_2Cl_2)→ $HO(CH_2)_{16}OAc$

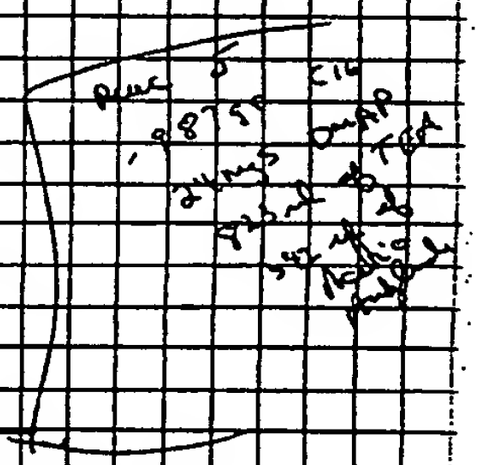
3.00 gs of $HO(CH_2)_{16}OH$

70 mgs DMAP

2.49 mls TEA

1.02 mls of Acetic Anhydride

400 ml RBF / 60 mls of CH_2Cl_2



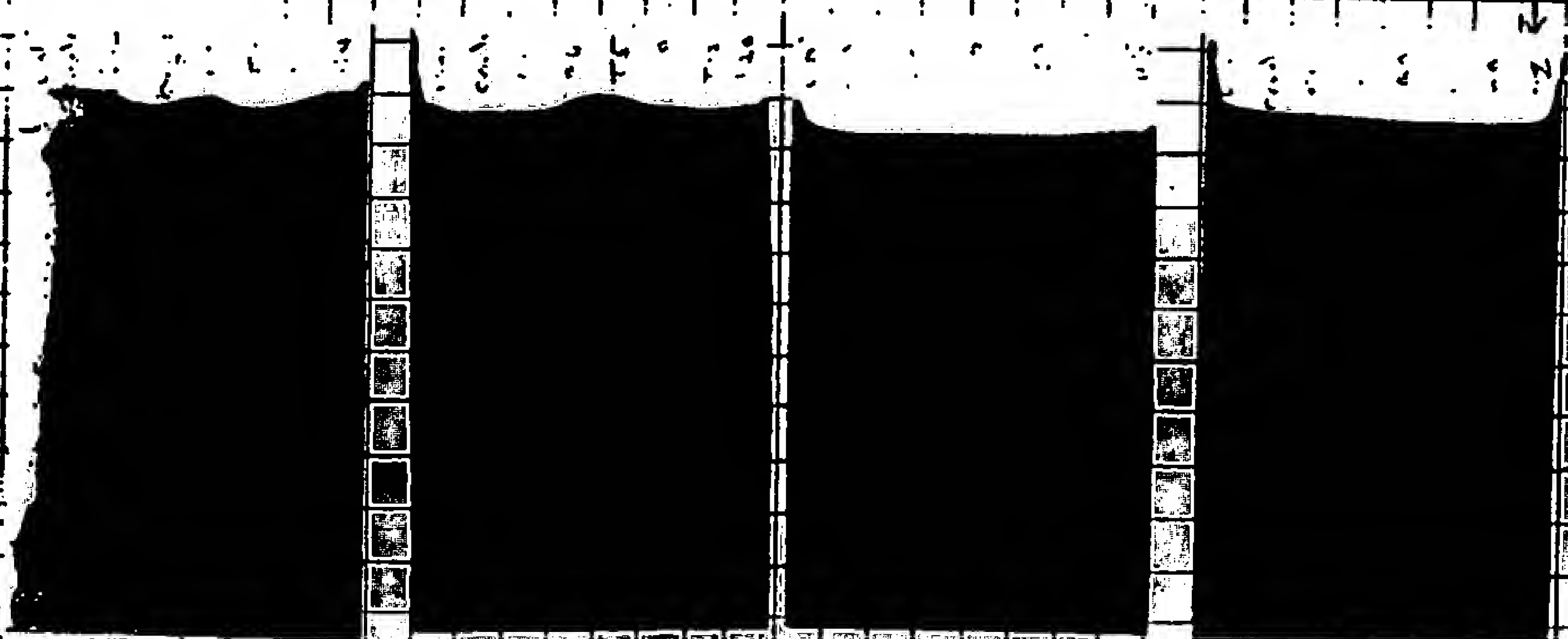
Reac. 4 1.4 gs of $HO(CH_2)_{16}OH$
33 mgs DMAP 484 ml Acetic Anhydride
1.2 mls TEA

Rxn B

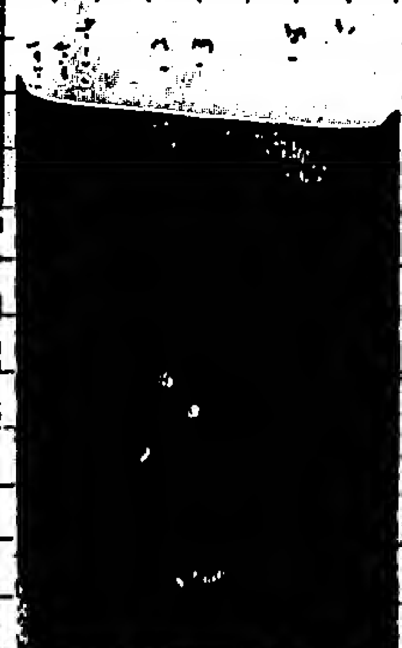
OH$(CH_2)_{16}$OH + Acetic Anhydride $\xrightarrow[CH_2Cl_2]{DMAP, TEA}$

1.37 gr of Diol was slurried in 25 ml of Dry CH_2Cl_2. 0.5 equiv of DMAP (32.33 mgs) was added and 1.4 equiv of TEA (1.14 mls) and 476 µl of Acetic Anhydride

Tube 72



50 ml solvent front [illegible] diol .08
12 mm monoacetate = .25
35 mm diacetate = Rf .07



The flash column was 250 mls of silica. 1.2 liters of 80:20 hex/Ether was passed through and the gradient [illegible] up to 55:45. After tube 72 it took [illegible] 200 mls of 50:50 to remove all the product

$C_{18}H_{36}O_3$
300.93

C15H32 ~S

$HO(CH_2)_{16}OAc$ + p-TsCl ⟶ HO TsO$(CH_2)_{16}OAc$

Fieser + Fieser page 1180

500mg (1.7x10^{-3} moles) of $HO(CH_2)_{16}OCCH_3$ (C=O) in in dry pyridine and in 50 ml erlenmeyer flask and cooled to 0°C, & TosCl (190.65) in 1 molar excess (or 634 mgs) with a stirring bar and allowed to proceed for 40 hrs. The solution was poured into a beaker with 200mls of ice water and suction filtered and then ~~Solid~~ slurried in heptane (20) and rotovaped to

Rf

@ Solvent Front 48mm

Mono - 12mm - .25

TOS - 28mm - .58

⊕? ⟵

product

50:50 hexane Ether

[redacted]

→ TosCl

→ mono acetate

Diol

The product spot is UV active and densin active. Presumably the H_2SO_4 in the CAM hydrolyzes the Ac on TOS ~~to~~ giving the (+) reaction

dryness. H'NMR is consistent with the proposed structure

[redacted]

Repeat

Rf AcO-$(CH_2)_{16}$-OH + Cl-SO_2-⟨benzene⟩-CH_3 ⟶

Solvent Front = 47

TOS 27.5

Rf: 0.59

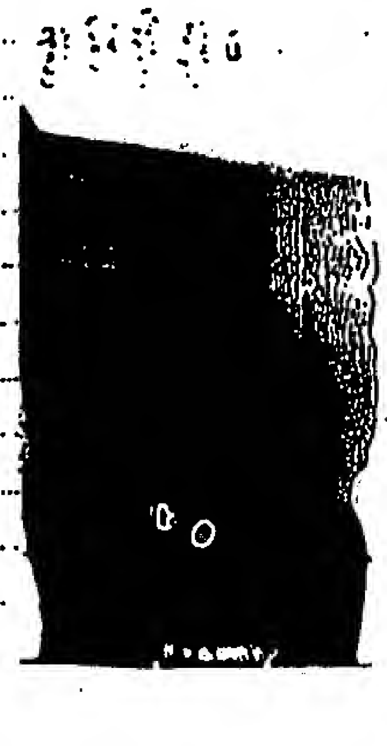
Total 17 + .36 MW

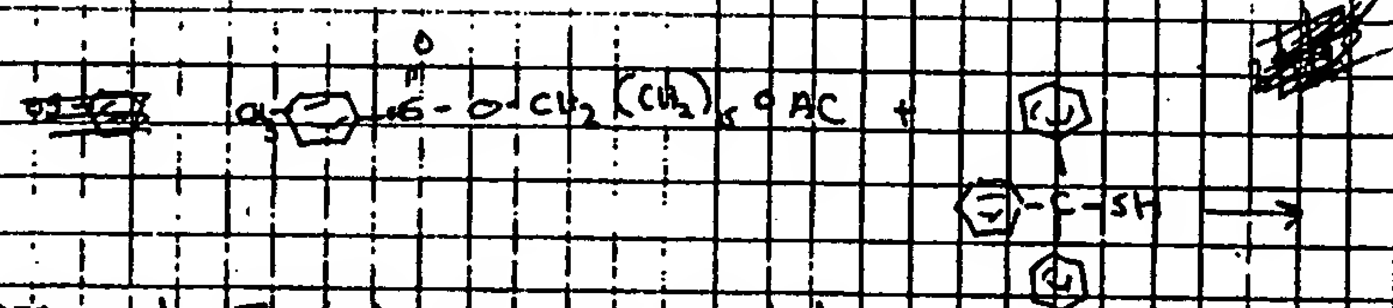
$CH_3\overset{O}{C}O$-$(CH_2)_{16}$-OSO_2-⟨benzene⟩-CH_3

~~$C_{25}H_{42}O_6S$ = 454.72~~

$C_{25}H_{42}O_5S$ = 438.72

− 15.998





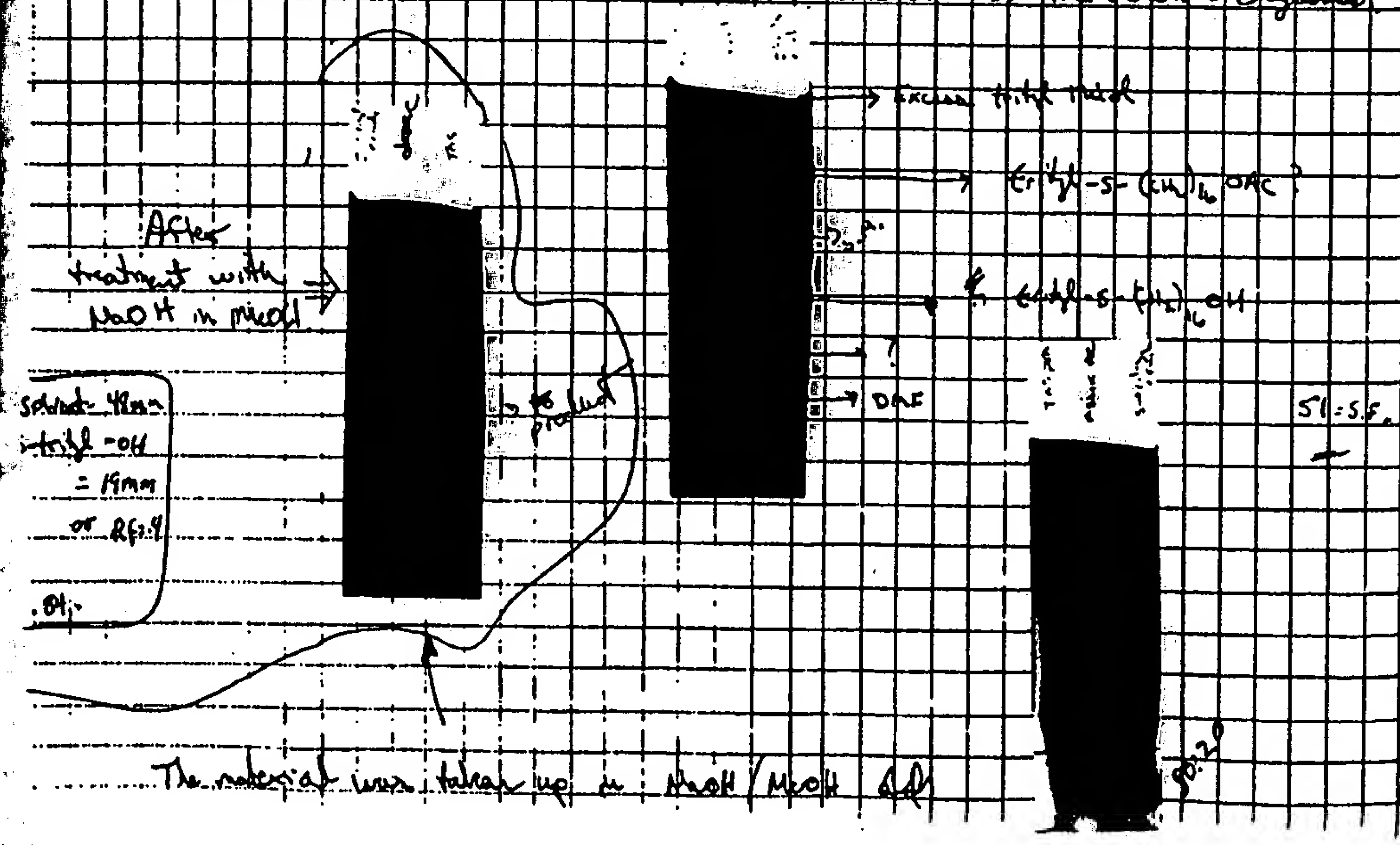
370 mg of $TsO(CH_2)_{16}OAc$ was dissolved in 10 ml of DMF and thoroughly degassed on the vac. line

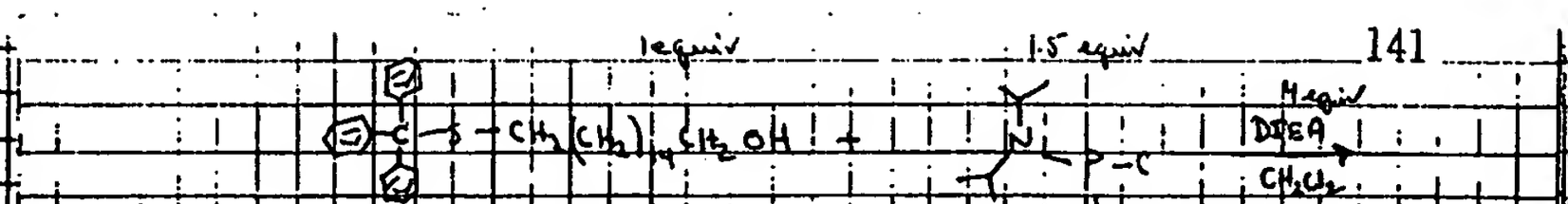
(mw = 454.72 or 8.1 x 10^{-4} moles)

NaOH - 40

- Triphenyl methyl mercaptan (Mw 276.40 . 0.95 equiv c 7.7 x 10^{-4} moles = 213 mgs)
- 31.8 mgs of NaOH (.98 equiv) in ~~more~~ 180 ul of H_2O

5 mls of ethanol was degassed on the vac line and 213 mgs of trityl Thiol added. 180 ul of degassed NaOH in H_2O was added via syringe under Ar. To this solution 370 mg of $TsO(CH_2)_{16}OAc$ in DMF/EtOH was added and the solution degassed





1

$C_{34}H_{48}OS$ - MW 504.87

- 220 mgs of 1 = 4.4×10^{-4} moles
- 6.5×10^{-4} moles of phosphoramidite 236.68 d = 1.061 M = 4.48 moles
- 5.74 moles ~~2.0 x 10~~ 1.9×10^{-3} moles DIEA MW ~~99~~ 129.25 $\frac{0.742}{129.25}$ = 5.74 moles

220 mgs of 1 was slurried in 15 ml of dry CH_2Cl_2 and immediately 326 ml of DIEA was added. 145 ml of Cyanoethyl phosphoramidite was added dropwise. After 30 min and additional 50 ml of Cyanoethyl reagent was added.

Note:
TEA MUST be present during Flash!
∴ the addition of 1% TEA to the mobile phase, dry the diethyl Ether

[redacted]

142

$HO-(CH_2)_6-OAc$ / PTSCl ⟶ $TsO-(CH_2)_6-OAc$

57 gr of monoac product was slurried in 357 mls of dry pyridine and cooled to 0°C. 650 mg of TosCl was added and the reaction mixture allowed to proceed for 40 hrs.

Note:

Must use FRESH TBoCl

Total yield 130 mgs

50/50 Ether/Hexane

(516.89) 276.54

Trt-S-$(CH_2)_6$OH ⟶ HS-$(CH_2)_6$OH

~~200~~ 111mg of Trityl-S-$(CH_2)_6$OH (2.13×10^{-5} moles)

276.40
− 1.01
275.39 g

+
516.89

.3 ml
100 mM TEAE
100 mM $AgNO_3$
140 mM DTT

1 mg dissolved in 400µl (5 mls and adding TEAE buffer)

1 ml of $AgNO_3$ solution + 30 mM

1 ml of DTT + 30 mM (154.2 mM) .152g in 1 ml = 1M

.1 ml of 100 mM DTT or .1 ml of 1M DTT
1.1 ml of 100 mM $AgNO_3$ or 1 ml of 1M $AgNO_3$

[redacted]

NMR says NR. The majority of isolated material is strongly retained.

TsO—$(CH_2)_{16}$—OAc + NaSH —Dry DMF→

1.6 equiv

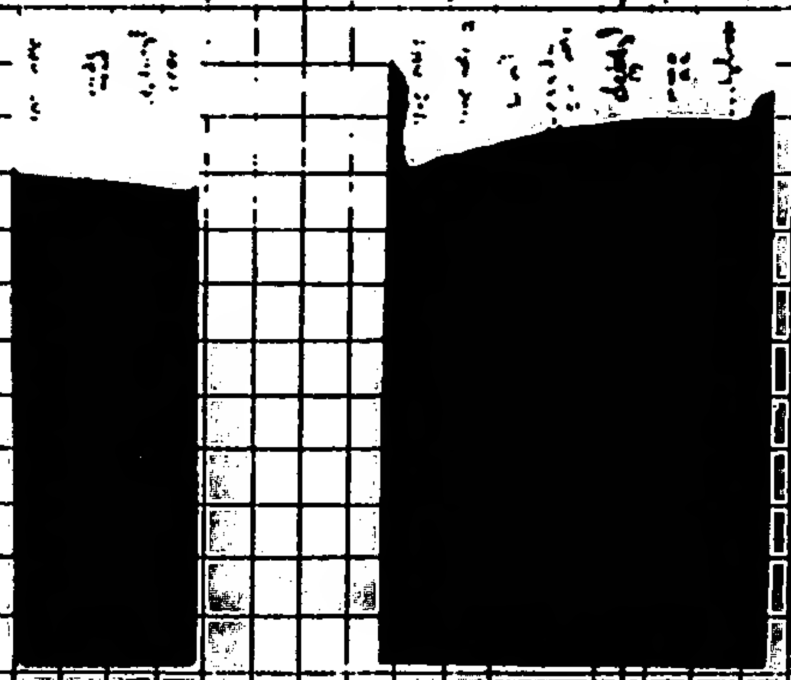
2 equiv

O. ⊕

MW = 454.72 [illegible] or 3.3×10^{-4}

or 18.4 mgs.

NaI + Anhydrous Acetone



50:50 Diethyl Ether : Hexane

NMR reveals that the spot detrityl ① is from the reaction of trityl-OH with $AgNO_3$ did not occur

NMR = trityl-OH NR

≈ 75 mgs Starting material = 1.7×10^{-4} moles x 1.2 equiv of NaSH

2×10^{-4} moles NaOH or 8 mgs dissolved in MeOH

50:50 diethyl Ether / Hexane

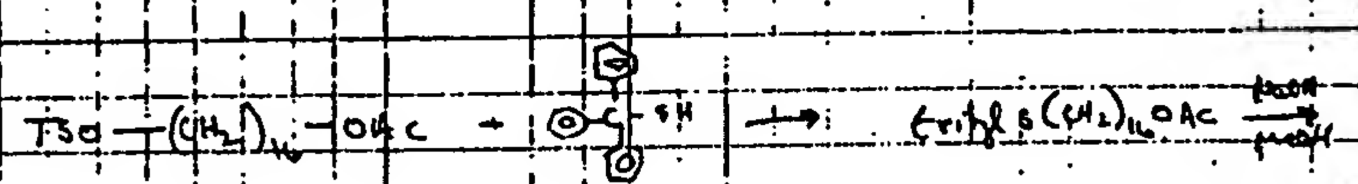
with "Anhydrous" NaSH

[redacted]

$OH-(CH_2)_{16}-OAc$ + Ptolsccl ⟶ $TsO(CH_2)_{16}-OAc$

2 x 250 mg or 8.5×10^{-4} moles in 15 mls of dry pyridine is cooled to 0°C in an ice bath. 320 mgs of TsOCl is added and the reaction allowed to proceed @ 4°C. The product (brownish tint) is poured into a beaker with bowls of ice water, stirred for 10 min and filtered. The solid is washed with water and dissolved in pet ether and charcoal added with stirring. The mixture was filtered and dried (400 mgs total)

24 hours is not long enough, some OAc remains



325 mgs (mw = 454.72) or 7.115×10^{-4} moles was dissolved in 10 mls of dry DMF and degassed. Triphenyl methyl mercaptan (mw 276.4) with 1.1 equiv (7.86×10^{-4}) or 217 mgs ~~and~~ 1.05 equiv of NaOH or 30 mgs was dissolved in 150 ul of H_2O and degassed.

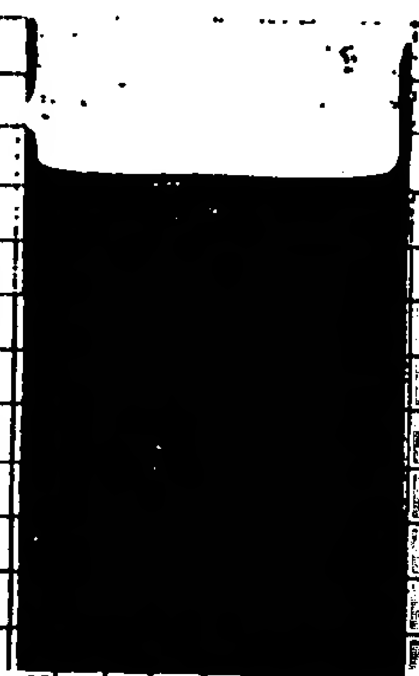
[redacted]

The trityl SH was dissolved in 5 mls of EtOH and degassed. The NaOH was added via syringe and then ~~the~~ to the TsO-OAc ~~added~~. The reaction was repeatedly degassed and allowed to proceed for 12 hrs.

The reaction was TLC, and NaOH/MeOH added to chromatography.

⟹ Flash ⟶ phosphoramidite

EtoAc



{JOC, 1966, V31, 1158} trityl-S$(CH_2)_{10}$-OH ⟶ SH$(CH_2)_{10}$OH

mw = 516.89

25 mgs (4.8 × 10⁻⁵ moles) was dissolved in glacial acetic acid (1.15 ml) and .38 mls of 1N HCl added. The reaction was allowed to stir for 1.5 hrs and 75°C. Upon addition of 1N, the material formed a white ppt immediately. After warming for ~ 5 min the ppt redissolved with the resulting solution slightly cloudy

TOS-(4H2)$_{10}$-CH$_2$Cl $\xrightarrow[\text{NaOH}]{\text{Dry DMF}}$

MW = 4697.72

@ 65 mg of the TOS derivative was dissolved in 5 ml of dry DMF

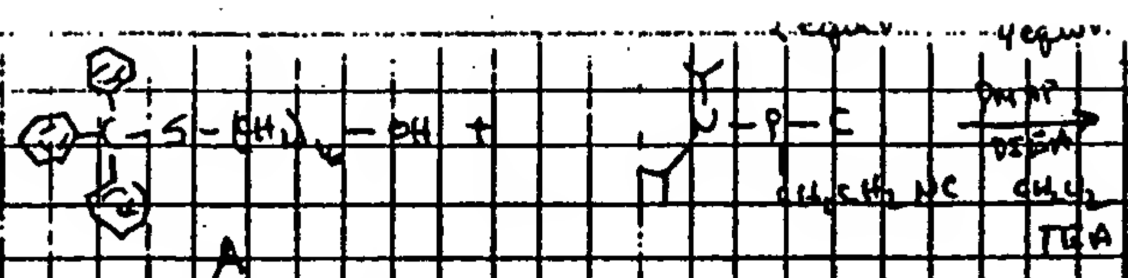
1.4×10^{-4} moles x 2 equiv of NaSH or 2.9×10^{-4} moles or 17 mgs

mass of NaOH is dissolved in 1 ml of dry MeOH. The NaSH

(in 2 mls of dry MeOH) was degassed and the NaOH added.

This solution is added (via syringe to the dry DMF TOS

product



170 mgs of A = 3.4x10^{-4} moles

151 µl or 2 equiv of phosphoramidite

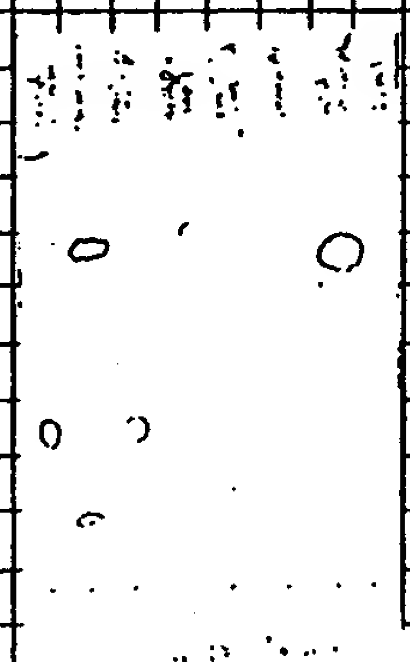
240 µl 10 of DIEA.

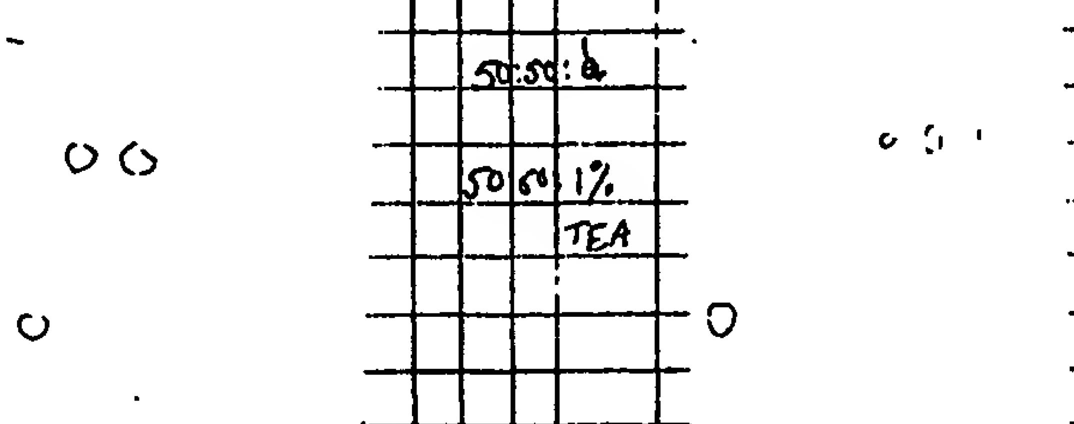
170 mgs of A was dissolved in ~~30 ml~~ 15 mls of CH_2Cl_2 and 240 µl of DIEA added. 151 µl of phosphoramidite was added dropwise over 30 min. The column was run with

90:10:0.5

Hex:Diethyl Ether:TEA

200 mls of resin





product →

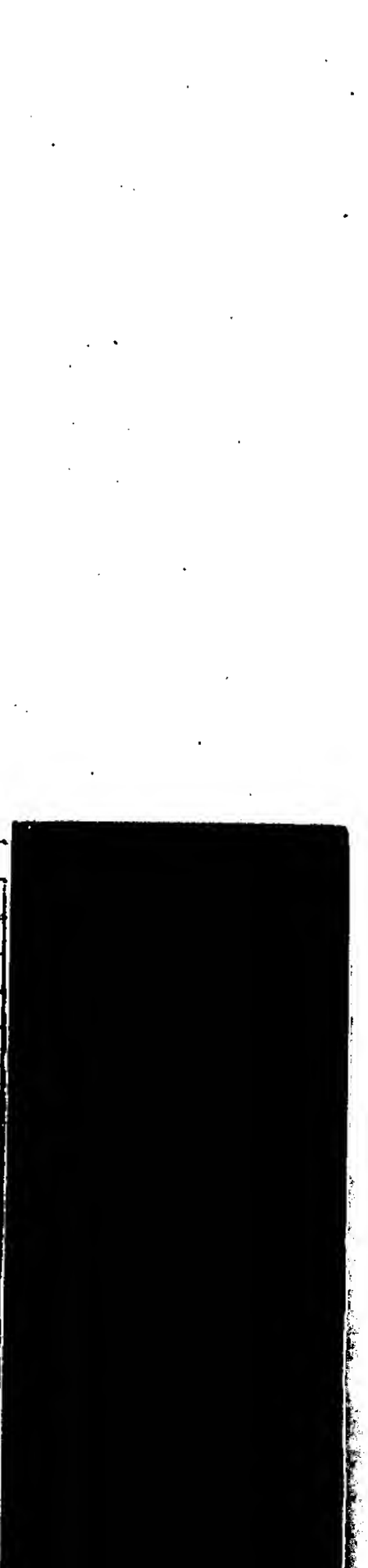
trityl →

isolated

≈ 125 mgs

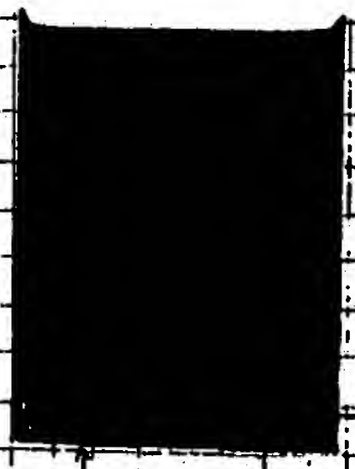
[illegible]

Spotted = 40 min



- A plate using Ce Ammonium Cerium Nitrate revealed on the presence of DTT

After cooling a white ppt. formed all the solution was dissolved in 100 ml of CH_2Cl_2. pH Na_2CO_3 (5M, pH 9) was used to wash with the CH_2Cl_2. The reaction was extracted with the water layer was pH 8. The solution was then washed with pH 7 buffer & rotavaped to dryness



→ Before back wash

└ After washing (neutralized) with pH 8 Na_2CO_3

poly-d-lysine (mw 25,000) + DTPA Anhydride →

Poly lysine was dissolved in DD H$_2$O and (120 mgs in 2 mls) and applied to a PD-10. An additional 1/2 ml was added and 3 mls total collected from each of 3 PD-10 columns. The recovered dried material (≈ 65 mgs) was divided into 3 reaction vessels of 22 mgs each.

The following ratios will be prepared: 50x, 100x, 200x

(See page 100 + 101)

0.1 mM Poly-d-lysine:

22 mg (8.6 x 10^{-7} moles) in 8.6 mls = 0.1 mM

∴

50x DTPA Anhydride or {4.3 x 10^{-5} x 357.3 = 15.4 mgs

100x or {8.6 x 10^{-5} x 357.3 = 30.7 mgs

200x or {1.72 x 10^{-4} x 357.3 = 61.5 mgs

0.5 M HCO$_3$ buffer ; pH ≈ 9.5

Only the 200x reaction showed any change in pH (e.g. → 9.4)

The reaction was ~~[illegible]~~ spread equal to dialysis

400X

35.2 mg or 1.4 x 10^{-6} moles

200 mg of DTPA Anhydride in 14 mls pH 9.5 HCO$_3$ Buffer

$OH(CH_2)_{10}OH$ + Acetic Anhydride $\xrightarrow[TEA]{DMAP}$ CH_3CH_2

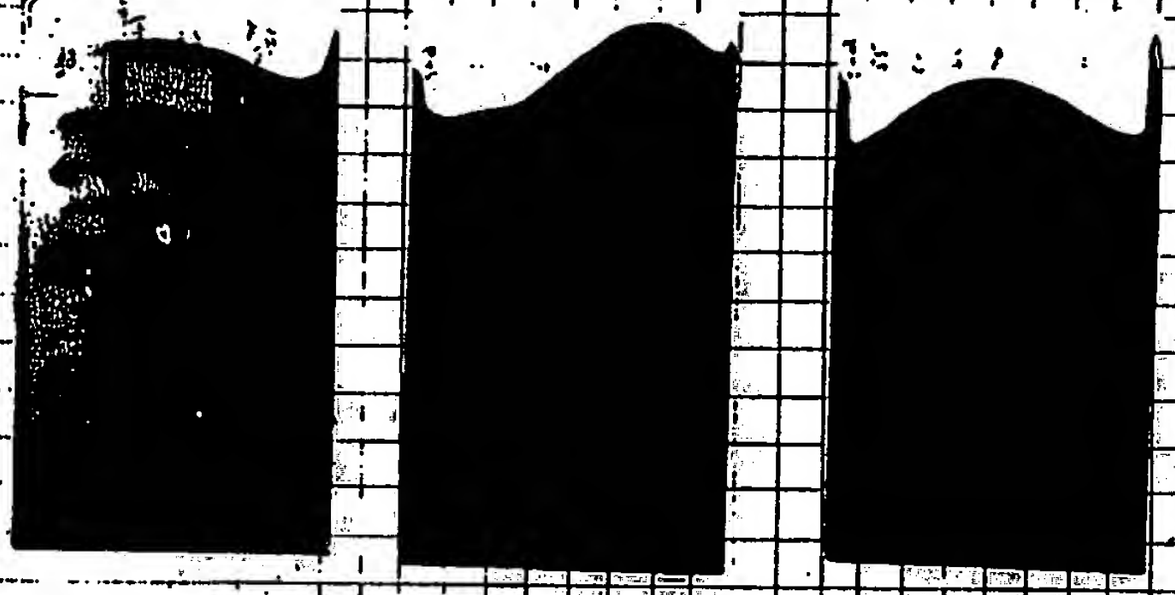
(258.96)

3 gs of diol was stirred in 50mls of Dry CH_2Cl_2 and
≈ 7½ mgs of DMAP added along with 2.5 mls of TEA
and 1.04 mls of Acetic Anhydride

$OH(CH_2)_{10}OH$ + PTsOCl ⟶ TsO — OH

2 gs of ($OH(CH_2)_{10}OH$; 7.74×10^{-3} moles) was dissolved in 50 mls
of dry pyridine and cooled to 5°C. TsCl (190.65) 1equiv
= 1.48 gms was added and the reaction allowed to proceed
for

TOS—C16—OAc Purification



The water/py solution is evaporated to dryness and shaken in heptane/diethyl ether and evaporated 3 times. The solid is dissolved in 50:50 EtOH:water and filtered. The solution is applied to a column 95:5 hexane:EtOAc. Plate 2 reveals impurity. Future: Run 90:10 to start and run up to 80:20

See page 135 for prep.

Tos — C_{16} — OAc + NaI $\xrightarrow[\Delta\ 50°C]{Acetone}$ I — C_{16} — OAc

180 mg ~~170~~ ~~150~~

~~239~~ mg of Tos — OAc (MW = 454.72) ~~or~~ of 4.0 (~~3.3~~) $\times 10^{-4}$ (~~5.2 $\times 10^{-4}$~~) moles is dissolved in anhydrous Acetone and a 100x (50) or 4×10^{-2} (~~3.3×10^{-2}~~, ~~6.2×10^{-1}~~) moles or 3 grams (~~...~~) (mw 149.89) of NaI added. The reaction is followed by TLC. After 15 min a crystalline material began to ppt out

[redacted]

~~...~~ I — $(CH_2)_{16}$ — $OC(=O)CH_3$ + NaSH $\xrightarrow[heat]{EtOH}$ SH — C_{16} — OH

[redacted]

50 mgs of I$(CH_2)_{16}$OAc was dissolved in ~5 mls of ETOH. 75 mgs of NaSH (10x) was slurried in 20mls of ETOH and the Iodide added slowly and kept at ~60°C for 2 hrs.